REMARKS

Status of the Claims

Claims 65 and 70-83 are pending, with claims 80 and 82 being independent. Claims 65 and 73-75 are canceled herein without prejudice or disclaimer thereto. Applicants reserve the right to file at least one continuation application directed to any subject matter canceled by way of the present Amendment. Claims 71 and 82 are amended herein. Claim 71 is amended with regard to viscosity, and claim 82 is amended to recite the subject matter of claim 65. Claim 84 is added. Support for the claim amendments and new claim can be found throughout the specification and claims as filed. As such, no new matter has been added.

Applicants note with appreciation that the rejections of claim 79 under 35 U.S.C. § 112, first and second paragraph, and claims 61-63, 65-66, 68, 72, 76-77 under 35 U.S.C. § 102 over Yajima et al. and claims 61-68, 76-78, 80-81 under 35 U.S.C. § 102 over Briskin have been withdrawn.

In the Office Action, the Office states that priority has not yet been perfected. Applicants request clarification. In the Office Action of July 3, 2002, the Examiner had stated that the priority document, (Slovenia P-9900030) had not been provided. In the response to the Office Action of January 3, 2003, Applicant noted that the document was confirmed as received by the PCT March 8, 2000. This is confirmed by the Notice Concerning Transmission of Priority Document issued by the International Bureau. As priority appears to be complete, this application should be entitled to a priority date of February 19, 1999.

Applicants respectfully request the Examiner to reconsider and withdraw the outstanding rejections in view of the foregoing amendments and the following remarks.

Rejections under 35 U.S.C. § 103

Claims 65, 72-73, 76-78 and 80-83 stand rejected under 35 U.S.C. § 103 as purportedly unpatentable over Briskin (WO 95/22319) in view of Gibson (USP 5,811,120).

Briskin in combination with Gibson fails to recite or even to suggest the claimed invention. Before turning to the cited references, Applicants note that the present invention is directed to pharmaceutical formulations which provide a therapeutic effect for over about 24 hours, as the presently claimed formulation is able to provide 24 hour release of the clarithromycin or clarithromycin derivative through a dual matrix system. The hydroxypropyl methylcellulose forms a viscous layer through which the clarithromycin or clarithromycin derivative is diffused, releasing the active ingredient over about a 24 hour period.

Briskin does not disclose the claimed cumulative pharmaceutical formulation with the 24 hour dosage effect. The Office states that "Briskin ... suggests the combination of a hydrophilic polymer and a fatty component." However, this is not the case, as Briskin does not suggest any combination of a hydrophilic polymer and a fatty component which would result in a formulation having the properties of the present invention. Instead, Briskin merely but simply lists ingredients components among others which when mixed together do not result in the present matrix formulation having the same release profile and controlled release effect.

The presence of ingredients in the formulations of Briskin does not automatically result in formulations having the same controlled release properties recited in the present claims. The amounts and ratios of components used are all relevant to the resulting formulation. As noted, hydroxypropyl

methylcellulose is used to form a viscous layer, and the active ingredient, clarithromycin or a clarithromycin derivative, is diffused through the viscous layer. Thus, HPMC is used by the present invention to form the matrix, and is not used as a binder. Mixing, sieving and granulating ingredients together will not necessarily result in the formation of a matrix if the proper ingredients in the proper amounts are not put through the proper process. The mere presence in Briskin of HPC and a fatty component, does not result in the present matrix.

Further, Applicants note that the amounts of components cited by Briskin are not the same as those of the present invention. Accordingly, the formulation of Briskin will not have the same properties as the claimed formulation. For example, the Office compares the present invention with Example 1b of Briskin. However, the formulation of the present invention contains over 17 % of HPMC whereas in the example 1b only discloses 5 % HPMC.

The Office states that "Briskin utilizes the same" amount of glyceryl behenate. However, the amount of glycerol behenate of the present invention is 21.5%, where Briskin discloses 10 % (see p.8), which is less than half of the present invention. Moreover the glyceryl behenate has been added to the formulation of Briskin as an extrusion aid, and is not combined with particular ingredients in the formation of a matrix.

The Office further cites "1-75 % of glyceryl behenate". However, this is not a tenable amount when considering a controlled release formulation. No controlled release is possible with 1 % glycerol behenate. With 75 % of glyceryl behenate, clarithromycin may be trapped and never released. Attached are comparative dissolution profiles to further illustrate this point. Thus, when the Office states that the same components are present in the cited reference and the present invention, this range has no meaning. The particular amounts and combinations of the present invention are what is important and what provides the matrix and dissolution rate.

Gibson does not address these deficiencies. Gibson is cited as disclosing hydrophilic binders. The Office argues it would be obvious to substitute Briskin's binders with those of Gibson. However, Applicants again submit that the HPMC of the present invention is not used as a binder, but as a controlled release matrix forming agent. Combining the ingredients as in Gibson with Briskin will not result in the present matrix having controlled release abilities over a 24 hour period. Simply substituting one ingredient for another, without considering the other aspects of preparing a formulation, will not be sufficient to result in the same formulation of the present claims.

In light of the above, Applicants respectfully request that the rejections under 35 U.S.C. § 103 be withdrawn.

Claims 70-71 stand rejected under 35 U.S.C. § 103 as purportedly unpatentable over Briskin (WO 95/22319) in view of Gibson (USP 5,811,120) in further view of Evenstad (USP 5,126,145). The Office states that Evenstad further discloses the use of high viscosity HPMC for sustained release and uses HPMC under 100 cps as a binder.

As noted above, Briskin fails to disclose the claimed sustained release matrix effective over a 24 hour period. Both Gibson and Evenstad fail to remedy this deficiency. Briskin and Gibson are discussed above. Evenstad is cited as merely disclosing a controlled release tablet and the use of low viscosity HPMC, a viscosity less than 100 cps. In light of the above, Applicants respectfully request that the rejections under 35 U.S.C. § 103 be withdrawn.

Claims 74-75 stand rejected under 35 U.S.C. § 103 as purportedly unpatentable over Briskin (WO 95/22319) in view of Gibson (USP 5,811,120) in further view of Curatolo (USP 5,605,889). Claims 74-75 are canceled herein without prejudice or disclaimer thereto. Accordingly, this rejection is moot.

Claim 79 stands rejected under 35 U.S.C. § 103 as purportedly unpatentable over Briskin (WO 95/22319) in view of Gibson (USP 5,811,120) in further view of Khan (USP 5,656,296). The Office argues that Khan, as a secondary reference, discloses a coating for sustained release.

However, Applicants again note that the controlled release properties of the present invention are imparted by the hydrophilic lipid matrix, and not by the presence of a coating. Thus, the presence of a sustained release coating in the disclosure of Khan does not remedy the deficiencies of Brisking and Gibson.

In light of the above, Applicants respectfully request that the rejections under 35 U.S.C. § 103 be withdrawn.

Claims 65, 70-72, and 76-83 stand rejected under 35 U.S.C. § 103 as purportedly unpatentable over Akiyama (WO 98/43211) in view of Farah (USP 6,194,005).

The present invention is directed to pharmaceutical formulations which provide a therapeutic effect for over about 24 hours, as the presently claimed formulation is able to provide 24 hour release of the clarithromycin or clarithromycin derivative. As discussed, the hydroxypropyl methylcellulose forms a viscous layer through which the active ingredient is diffused, releasing the active ingredient over about a 24 hour period.

None of the disclosure of Akiyama is related to a sustained release composition, and certainly not to a dual matrix sustained release formulation containing clarithromycin and HPMC. Instead, clarithromycin and HPMC are merely listed amount many other substances and excipients. Moreover Akiyama aims to keep the formulation for a longer time in the stomach for healing of ulcers, and thus is not targeted or intended for sustained release as with the present invention. Dissolution profiles are not discussed.

Farah does not remedy these deficiencies. Farah discloses a 720 minute,12 hour release or twice daily administration. This is a different formulation intended for a different release profile and different purpose from the 24 hour controlled release formulation of the present invention, which only needs to be administered once a day. Applicants further note that the amount of lipids disclosed by Farah is lower than that of the present invention (1-15 % versus 21.5 %).

In light of the above, Applicants respectfully request that the rejections under 35 U.S.C. § 103 be withdrawn.

Claims 74-75 stand rejected under 35 U.S.C. § 103 as purportedly unpatentable over Akiyama (WO 98/43211) in view of Farah (USP 6,194,005) in further view of Curatolo (USP 5,605,889). Claims 74-75 are canceled herein without prejudice or disclaimer thereto. Accordingly, this rejection is moot.

Claim 73 stands rejected under 35 U.S.C. § 103 as purportedly unpatentable over Akiyama (WO 98/43211) in view of Farah (USP 6,194,005) in further view of Gibson (USP 5,811,120). Claim 73 is canceled herein without prejudice or disclaimer thereto. Accordingly, this rejection is moot.

CONCLUSION

If there are any questions regarding this amendment or the application in general, a telephone call to the undersigned would be appreciated since this should expedite the prosecution of the application for all concerned.

If necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response, and

please charge any deficiency in fees or credit any overpayments to Deposit Account No. 05-1323 (Docket #99380.B480017).

Respectfully submitted,

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